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PREOPERATIVE PSYCHOLOGICAL STATE AND THE ADRENAL RESPONSE TO SURGERY

JONATHAN J. RUSS

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Preoperative Psychological State

and the

Adrenal Response to Surgery

by

Jonathan J. Russ, A.B.

A Thesis

Submitted to the Faculty

of the

Yale University School of Medicine

In Candidacy for the Degree of

Doctor of Medicine

The Department of Psychiatry

School of Medicine, Yale University

1964

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For L

Fallen as the time drops slow behind
We stand before the canyon and the cliff
And echo out the sounding of the mind
Rearing granite now. To find its mounding
Tendencies, then, mount the skull as if
Its vertices domed lower than the black
That gasps above its nostril-scenting sea.

ACKNOWLEDGMENTS

This study could not have been executed without the assistance and co-operation of a number of individuals.

I should like to thank Dr. Ben Bursten for his supervision and guidance from the inception of the planning of this work to the completion of its writing, and also for obtaining financial support for the typing of the interviews. Without his persistent adherence to rigorous standards of proceedure and thought, this thesis could not have reached its present form.

Dr. Thomas T. Amatruda was unstinting of his advice concerning the metabolic problems involved in this research, and also in supplying laboratory facilities with which to carry out the necessary laboratory work. The staff of his metabolic research laboratory was most helpful in aiding the author in learning the proceedures of the plasma cortisol determination, and in carrying out themselves the urine ketogenic steroid determinations.

Dr. Robert K. Marvin and the Department of Anesthesiology at the West Haven V. A. Hospital were of great help in controlling the type and length of anesthesia, and in assisting in drawing the blood sample taken while the patient was ungoing surgery.

Finally, I should like to thank Dr. W. W. Lindemuth and the surgical staff at the West Haven V. A. Hospital for consenting to this work with their patients and for whenever possible predicting herniorraphies several days in advance of operation. The nursing staff was instrumental in achieving a remarkably high proportion of successful 24 hour urine collections.

J. J. R.

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PREOPERATIVE PSYCHOLOGICAL STATE AND THE ADRENAL RESPONSE TO SURGERY

INTRODUCTION

It is well known that the physical stress of surgical operation can induce an increase in adrenocortical activity to many times the basal levels in patients with normal endocrine systems.[15,21,27,28,35,41,51,53,57,62] It is also known that emotional stress, including preoperative emotional state, is capable of affecting corticosteroid levels independently of physical trauma,[4,8,19,22,26,37,47,48,50,52] although values remain "within the normal physiological range."[4] It is the purpose of this thesis to investigate the possibility that preoperative psychological states affect adrenocortical activity during and after surgical proceedures.

Steroids and Psychological Factors

Although other substances present in the body have been found to correlate well with measurements of certain emotional states, in recent years investigators have tended to concentrate their attention on the hormones synthesized by the adrenal cortex, particularly hydro-

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Steroids and Psychological Factors

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cortisone (compound F, cortisol). Even before techniques for determining corticosteroid concentrations were widely available, it was known that parameters dependent on adrenocortical function such as salivary Na/K ratio[33] and blood eosinophil levels[13] were affected by psychological stresses. Dreyfuss and Feldman[13] found a 44% drop in the average eosinophil level in medical students awaiting examination, and hypothesized that emotions act through the hypothalamic-pituitary-adrenocortical route to produce an increase in corticosteroid levels in the body analogous to that attained as a result of physical stresses.

More direct estimations of adrenocortical activity have been made using techniques capable of measuring the concentration of corticosteroids and their metabolic products in the urine (17-OH corticosteroids, 17-ketogenic steroids) and in the blood (17-OHCS, 11OHCS).[56] In all of the blood determinations, cortisol is the major component measured, but the absolute concentrations recorded vary with the particular method used (acid fluorescence, phenylhydrazine reaction, etc.) and it is therefore not possible to compare directly the levels measured by various investigators.

There is evidence that even the process of collecting blood samples may cause a significant elevation of cortisol levels in the blood of subjects. Davis and co-workers[8] found mean serum cortisol levels in the blood of subjects undergoing an anticipated unknown proceedure (venipuncture) to be significantly higher than the second time

cortisone (compound 4, cortisol). Even before techniques for determining corticosteroid concentrations were widely available, it was known that parameters dependent on adrenocortical function such as salivary Na/K ratio[35] and blood eosinophil levels[36] were affected by psychological stresses. Dreyfuss and Fuldman[37] found a [illegible] in the average eosinophil level in medical students [illegible] [illegible], and hypothesized that emotions act through the hypothalamic-pituitary-adrenocortical route to produce an increase in corticosteroid levels in the body analogous to that attained as a result of physical stresses.

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There is evidence that even the process of collecting blood samples may cause a significant elevation of cortisol levels in the blood of subjects. Davis and co-workers[6] found mean serum cortisol levels in the blood of subjects undergoing an anticipated unknown procedure (venipuncture) to be significantly higher than the second [illegible]

the same--by then familiar-- proceedure was performed. Although they relate this finding to a "first time effect," it would seem more accurate to attribute it to anxiety over the concealed nature of the proceedure, rather than to the fact that it was a new experience. They did, in fact, find a correlation of +.64, significant at the 0.02 level, between the cortisol levels of the individual subjects and their scores on the Sarason general anxiety test.

Many workers have found that anxious subjects tend to have higher corticosteroid levels than non-anxious controls. Persky et. al.[47] found plasma and urinary hydrocortisone concentrations to average 60-70% greater in subjects judged anxious by psychiatric interview than in those not considered anxious. Fiorica and Muehl[19] compared the plasma cortisol levels of nineteen subjects achieving high scores on the Taylor Manifest Anxiety Scale with the cortisol levels of thirty-one low-scoring subjects, and found the former to be significantly higher (0.005 level) than the latter. The relationship between elevated corticosteroid levels and anxiety is widely accepted.[4,22,48,52]

There is less evidence to indicate that corticoid levels may be lowered, as well as elevated, by psychological factors. Handlon et. al.[26] found that subjects viewing certain dull and relaxing films responded with a lowering of steroid levels, and suggested that the adrenal cortex responds to events of emotional significance in ordinary experience by raising or lowering of plasma corticosteroids. Occasional fall of these corticoids to extremely low levels (0-3%) has been more

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recently noted to occur in deep hypnotic trances,[55] tending to return to normal levels within 90 minutes after termination of the trance. There is no agreement among experimenters about factors that may depress steroid levels. Bliss[4] found that monotonous and repetitive tasks did not significantly change plasma cortisol concentrations. Depression and psychomotor retardation have been found to be associated with elevated, rather than decreased, corticosteroid concentrations.[6,13]

As evidence accumulates it appears that psychological turmoil, rather than anxiety alone, is the psychic state that is best correlated with steroid level elevations. Eosinopenia-- a sensitive indication of cortisol elevation-- has been reported to occur in manic-depressive patients during depression, as well as agitation.[13] Sachar et. al.,[54] in a psychiatric and endocrine study of four acutely psychotic patients extending over a period of months, found elevations of steroid levels in blood and urine to occur during periods of excitement and depression, and reported normal levels during recovery and "psychotic equilibrium." These findings are consistent with the fact that steroid levels are generally normal in chronic schizophrenic patients.[3,4] It seems that corticosteroid concentrations are more influenced by the effectiveness of the psychological defenses used by the individual than by the particular type of psychological defense used. Previous work (Bursten[5]) has shown that inadequacy of coping mechanisms may be associated with a predictable physiological response, whether the psychological distress

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is manifested by agitation or by depression.

Psychological factors may cause changes in patterns of corticosteroid levels in the blood as well as changes in the levels alone. Kral[33] found that abnormal diurnal patterns of steroid-dependent values (eosinophil count and salivary Na/K) were most likely to occur in patients for whom there was difficulty in making a psychiatric diagnosis. Persky, Grinker and co-workers[47] noted that patients with high levels of anxiety showed less of an adrenocortical effect of additional psychological stress than did patients who were less anxious.

The general hypothesis of the workers in the study of these psychoendocrine relationships seems to have been that a psychological-cortical disturbance affects the adrenals by way of the hypothalamus and pituitary (ACTH)[47] with a tendency toward a direct relationship between the extent of the psychological stimulus and the adrenal response. This hypothesis cannot yet be regarded as proven, in the abscence of measured changes in ACTH secretion concomitant with psychological stress. The possible individual variations in steroid conjugation (liver), excretion (kidney), and even in physiological responsiveness to a psychological stimulus must also be borne in mind, although there is no way to allow for their effects in evaluating data. That these factors may be significant is shown by the impossibility of predicting in any single case what the steroid response to psychological stress will be. Bliss et. al.[4] persistently found a proportion of patients who were marked exceptions to their expectations,

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as in those subjects who had extremely low steroid levels at a time when they appeared extremely anxious. The cortical-hypothalamic-pituitary-adrenal explanation nevertheless is adequate to account for most of the data most of the time.

Steroids and Surgical Stress

Any consideration of variation of normal corticosteroids with stresses such as surgery must necessarily be evaluated against the background of normal variations in unstressed individuals. There are two types of variation involving blood cortisol levels ordinarily. The first is that of normal biological variation from individual to individual, which in the case of plasma cortisol determinations may encompass a normal range (8 a.m. samples) of about 10γ %, where the mean normal level is about 20γ% (see method section for further details). The second type of normal variation is temporal, consists of a diurnal variation in blood levels of cortisol, and seems to represent actual changes in the activity of the adrenals during each 24 hour period.[34] Normally, cortical activity of the adrenal is highest at 6-8 a.m. and lowest at about midnight.[11] This cyclic pattern is remarkably constant and resistant to change, and is usually unaltered by working night hours or by blindness.[40] Perkoff et. al.[46] found that in 51 normal subjects plasma 17-OH corticosteroids were lower at 4 a.m. than at 8 a.m. in all but one; lower at 4 p.m. than 8 a.m. in all but five; and lower at noon than at 8 a.m. in all but seven. These same workers found the daily

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variation to average about 8.5γ% in a group of subjects that averaged about 16γ% 8 a.m. levels. Thus it can be seen that the daily variation in plasma cortisol levels in a normal individual is about as great as the range of values among the majority of normal individuals. It is therefore obviously important to allow for the diurnal variation in attempting to draw conclusions about the significance of differences in the adrenal activity of experimental subjects. It has been demonstrated[59] that steroid levels elevated due to stress are still susceptible to the effects of diurnal changes, and the data of Sachar et. al.[54] show the same diurnal variation in patients with elevated plasma cortisol concomitant with psychosis.

After surgical trauma, burns, shock or other severe physical stress there is usually an increase in the concentration of corticosteroids circulating in the plasma. The length and extent of the operative proceedure tend to be related directly to the maximum plasma steroid concentrations reached after surgery.[57] Maximum levels are usually reached between four and twelve hours after operation,[35] but pronounced rises have been observed as early as one-half hour after incision.[66] Most workers have not taken blood samples between incision and one hour afterwards. Early uniform increase in plasma corticoids has been observed in patients undergoing severe operative trauma (thoracotomies and cholecystectomies). It is currently believed by most investigators that this response to surgery is caused by increased corticosteroid secretion under the influence of a greater ACTH stimulus,

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perhaps aided by retardation of the normal mechanisms of corticosteroid removal from the blood.[42] Actual increases in blood levels of ACTH have been measured during operation, and it has been found that in most patients maximal levels are found early in the course of the operation (one-half hour postincision).[7] Adrenal capacity does not limit the magnitude of the response, since it has been observed that administration of ACTH after operation will almost always cause an additional rise in plasma corticoids.[17,57] The corticosteroid response is also manifested in rises in urinary excretion of 17-OHCS which follow and are more prolonged than the changes in the blood,[35] as well as in secondary effects of elevated steroid levels, including negative nitrogen balance, eosinopenia, and changes in caloric consumption.[15,27,41,62] Plasma cortisol levels are generally again back to normal levels within 24 hours after operation.[35,62] Although the typical response to operation has been described above, it should be noted that some workers' data indicate that not all patients elevate their plasma corticosteroids in response to surgery;[36,57,67,71] some of them even show a drop. Most, but not all, of the patients who failed to show a rise in steroid level underwent a relatively minor operation such as herniorraphy.[67] Failure to show a rise was most common among, but not unique to, patients given spinal anesthesia.

The anesthesia used in preparing the patient for operation has, in itself, a significant effect on plasma corticosteroid concentrations, and one which varies with the agent used. The time elapsed from the

[illegible]

[illegible]

[illegible]

onset of anesthesia to time of operation tends to be directly related to the presurgical steroid level if ether is used, and to a lesser extent with N_2O and Halothane also.[36] There is apparently no blocking effect of deep surgical anesthesia on the neurohumoral reflexes involved in the elevation of corticosteroid levels, but spinal anesthesia probably blocks some of the afferent impulses necessary for a typical response to surgery (see above).[41,67,71] (Some authors report a good steroid response with spinal anesthesia,[35,57] but the reason for this discrepancy is unclear.) According to Viikari and Thomasson[66] all general anesthetic agents except ether cause a slight fall in corticosteroid concentration when the length of presurgical anesthesia is short. Data obtained after an hour of uninterrupted anesthesia[67] reveal a significant rise with ether, but only slight and inconsistent changes with cyclopropane, thiopental-N_2O and spinal anesthesias. In summarizing the effects of anesthesia on corticosteroid levels, it may be said that ether stimulates a marked rise, spinal probably interferes with the neurohumoral reflexes necessary for a normal response to surgery, and no other anesthetic agents cause a pronounced change, although there seems to be a tendency for an early drop in cortisol levels. Individual response to anesthesias other than ether varies, and cortisol levels in some patients may rise under the same conditions in which those in other patients fall.[36,66] It is at least theoretically possible that the changes occurring in corticosteroid levels during anesthesia are not a direct result of the effects of anesthesia itself, but may be due to interference with other

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The importance of the corticosteroid response to surgery is clear only in the uncommon case of its inadequacy, when the patient may go into irreversible shock.[21] In animals, a vigorous response has been associated with a good postoperative course, but in humans it is felt that a very wide range of responses is compatible with an uneventful convalescence.[51] Some workers believe that persistent postoperative elevation is related to an increased incidence of complications,[35] but no clear relationship between adrenal physiology and convalescent course has been established.

Psychological Factors and Surgery; Relation to Steroids

The relationships of psychological factors to surgical illness and operation are manifold, and may range from why a patient chooses to undergo operation[64] to why his symptoms may persist after he has been successfully operated on.[29] The segment of this subject with which this thesis is concerned is the psychological state of the patient during the preoperative period.

While awaiting surgery, the patient must face many types of threats, some actual and others symbolic. Janis[30] describes three major forms of actual imminent danger: acute pain, mutilation, and dying. Since there is little that the patient can do to directly influence or alter the nature of his actual danger, he is in the position of

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having to cope with it by psychological mechanisms, rather than by action.[30,39,65] Illness, hospitalization, and the passivity of the patient's role in surgery tend to foster functional and psychological regression,[39] and the degree of dependency may be little related to the patient's prior behavior or the degree of his actual danger.

The patient's preoperative psychological state is apt to be more a result of fantasied dangers than of the actual dangers of anesthesia and operation. These more intrapsychic threats are dependent on (1)the patient's premorbid personality, (2)the meaning of the impending operation to the patient, including his feelings about anesthesia and "incisional attack," and (3)the patient's emotional relationship to the surgeon,[10] as well as temporary changes in his economic, domestic, social and sexual patterns.[39] Both the anticipated anesthesia and operation lend themselves to unconscious ideation, with anesthesia often equated with death or loss of control of impulses[39] and operation itself with sadomasochistic fantasies.[30,39] The patient may have more specific fears of castration, separation or delivery,[65] particularly if the operation involves relevant areas of the body. Janis[30] notes that "a high level of preoperative fear appears especially likely if one faces hernia repair or hemorrhoidectomy and less likely if one faces an appendectomy."

As the result of the threats to the patient occasioned by the operation, real and imagined, conscious and unconscious, he experiences an anxiety signal.[10] This is usually dealt with by some degree of denial

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of the danger. As listed by Titchner[65] the levels of this denial are: (1)Suppression: The patient is aware of his operation and of his danger, but endeavors not to think about it. (2)Constriction of ego function: The patient will go to great lengths to avoid doing anything that might bring his true physical condition with its implications to his attention. (3)Repression: The patient becomes unaware of his physical state and/or impending treatment. (4)Complete denial: The patient actively denies his illness and asserts his health. Janis[30] lists four similar levels, but emphasizes the psychological means by which the patient achieves denial: (1)suppression of unpleasant thoughts, (2) isolation and repression, (3)rationalization and displacement, and (4) defensive dominance and negativism. The relationship of anxiety signal and successful denial to psychological stress in the preoperative patient is the key problem in the evaluation of patients with respect to the effect of psychological state on corticosteroid responses.

Elevated plasma corticoids have been found in preoperative patients. Franksson and Gemzell[22] took blood samples on the morning of surgery, and on the mornings of the two days before in 33 surgical patients. Twenty-six out of the group had a higher 17-OHCS level on the morning of operation than on either of the two days before, and only three failed to raise their level in the last 24 hour period. Mason[37] obtained similar results, and remarked that the elevations are "physiologically significant elevations which seem to characterize the response of healthy subjects to psychological stress." Not all

of the danger. As listed by Titchner[illegible] the levels of this denial are: (1)Suppression: The patient is aware of his operation and of his danger, but endeavors not to think about it. (2)Constriction of ego function: The patient will go to great lengths to avoid doing anything that might bring his true physical condition with its implications to his attention. (3)Repression: The patient becomes unaware of his physical state and/or impending treatment. (4)Complete denial: The patient actively denies his illness and asserts his health. Lewis[illegible] lists four similar levels, but emphasizes the psychological means by which the patient achieves denial: (1)suppression of unpleasant thoughts, (2) isolation and repression, (3)rationalization and displacement, and (4) defensive dominance and negativism. The relationship of anxiety signal and successful denial to psychological stress in the preoperative patient is the key problem in the evaluation of patients with respect to the effect of psychological state on corticostaroid responses.

Elevated plasma corticoids have been found in preoperative patients. Franksson and Genzell[illegible] took blood samples on the morning of surgery, and on the mornings of the two days before in 11 surgical patients. Twenty-six out of the group had a higher 17-OHCS level on the morning of operation than on either of the two days before, and only three failed to raise their level in the last 24 hour period. Mason[37] obtained similar results, and remarked that the elevations are "physiologically significant elevations which seem to characterize the response of healthy subjects to psychological stress." Not all

investigators have corroborated these findings, however, and some have reported that plasma cortisol levels on the morning of operation are not significantly higher than those of their control groups.[36,66]

In rating the psychological stress of preoperative patients most workers have evaluated anxiety.[52] Price, Thaler and Mason[50] found that "anxiety" was not an adequate description of the psychological state of their preoperative patients, whose "emotional responses were diverse," including states of resentful anger, active hostility--"high states of emotionality, but not always anxious ones."[50] They also demonstrated that other characteristics (as measured by Rorschach) including "unpleasant content" and "neutral content" (inverse correlation) correlated better with preoperative steroid levels than did "anxious content." They rated their patients on the basis of "discomfort-involvement" rather than anxiety. "Discomfort-involvement" was defined as a measure of emotional involvement including agitated depression as well as anxiety, a class of states in which "the clinical diagnosis was of relatively little importance when contrasted with the amount of feeling evidenced in the current situation."[50] Discomfort-involvement ratings made by psychiatrists and psychologists correlated with cortisol levels drawn on the day before operation at a better than 5% confidence level. The concept of discomfort-involvement would appear to be a reasonable description of the state of emotional turmoil found by other workers to be better correlated with elevated steroid levels than any single emotional state.

Investigators have demonstrated [illegible]

reported that plasma cortisol levels on the [illegible]

not significantly higher than those of [illegible].

In rating the [illegible] state of [illegible]

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including "unpleasant contents" and [illegible]

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any single emotional state.

HYPOTHESIS

Review of the literature reveals no previous study attempting to relate preoperative psychological state to changes in adrenal function during and after surgery. It was expected that the effects of surgery and psychological stress on steroid levels would tend to summate, and the hypotheses were therefore:

I Patients with higher degrees of discomfort-involvement (and/or with higher scores on a test of anxiety) will have a greater production of steroids during and after surgery than those with less discomfort-involvement or anxiety.

II Patients with higher degrees of "apathy-withdrawal" (essentially the reverse of discomfort-involvement, and partially derived from Engel's[16] concept of "depression-withdrawal" as a primary affect) and/or with higher scores on a test of depression, will have a lesser production of steroids during and after surgery than those with lower degrees of these psychological states.

MATERIALS AND METHODS

The Patients N=10

All patients were white males scheduled to undergo a unilateral

Review of the literature reveals no predictive study relating to relate psychiatric psychological scales to [illegible] drinking and alcohol [illegible]. It was suggested [illegible] and psychological [illegible] on alcohol [illegible] the hypotheses were therefore:

I. Subjects with higher [illegible] (and/or with higher social [illegible]) will have a greater proportion of [illegible] drinkers than those with lower [illegible] or drinking.

II. Subjects with higher [illegible] (generally the [illegible] [illegible] [illegible]

inguinal herniorraphy. They were screened by history and laboratory examinations for abscence of endocrine, liver and renal disease likely to interfere with normal production, metabolism and excretion of corticosteroids.[23]

The age of the patients was not limited. According to Samuels,[56] hormone levels (corticosteroids) in the blood are not significantly altered by aging, although there is a slight decrease in the maximal capacity to both produce and metabolize adrenal steroids in men over 65. Pincus confirms this statement,[49] but Nilsson et. al.[43] found patients over the age of 70 to have the same order of rises in plasma corticosteroids due to operation as younger ones.

Patient #:	1	2	3	4	5	6	7	8	9	10	mean age: 50
Age:	69	35	30	61	31	53	71	48	49	57	

The rank-order coefficient comparing ages of the patients with the change in plasma cortisol levels from just before the operation until the last sample taken (three hours later) is $r' = +.19$, statistically insignificant, indicating that the age of the subjects did not affect their response to surgery as manifested by plasma cortisol levels.

The Physical Stress

The patients were usually informed of the date of their operation on the day prior to it. They were routinely premedicated with seconal

[illegible] [illegible]. The [illegible] [illegible] [illegible]

and atropine, known not to cause significant changes in steroid levels.[43] Premedication was usually administered about one-half hour before the beginning of anesthesia, and although in some patients (those operated on early in the morning) it preceeded the drawing of blood for the 8 a.m. sample of the morning of operation, the data (appendix II, fig. 1) do not support the hypothesis that it may have lowered the cortisol levels in this sample from these patients due to sedation.

Anesthesia: Induction was achieved with pentothal, and the patient was then maintained with cyclopropane for the duration of the operation. Patients received succinyl choline during endotracheal intubation. One patient (#4) received maintainence intravenous insulin in a slow drip during operation. The time of presurgical anesthesia was always between 10 and 15 minutes.

Operation: The operative repairs were all unilateral, uncomplicated, and lasted between 1 hour 20 minutes and 1 hour 45 minutes. In the opinion of the surgeons, there was no unusual surgical trauma in any of the operations.

Herniorraphy was chosen because of (1)the relatively standard degree of physical trauma involved,(2)the relatively high degree of psychological stress likely to occur,[30] (3) the generally good state of health of the patients undergoing this elective proceedure, and (4) the frequency of the operation. Pentothal-cyclopropane anesthesia was chosen because it is not known to cause any significant change in cortisol levels (as does ether) or any interference with the typical adrenal

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response to surgery (as does spinal anesthesia).

The Psychological Parameters

Interview: The patients were interviewed on the evening before their scheduled operation. (In no case was the operation postponed.) They were encouraged to talk about the operation, particularly feelings of discomfort or uncertainty about it, and also about their tendencies to be "nervous," although the interviews were not rigidly structured, nor was there a fixed set of questions asked. The interviews were about 35 minutes average length, and an attempt was made not to intensify or allay the patient's feelings about the operation during the course of the interview. The interviews were recorded on tape, typed in duplicate, and evaluated as a group by two judges after all data had been gathered.

Ratings: The interviews were ranked by the two judges on the basis of discomfort-involvement as described by Price, et. al.[50] Patients were assigned no score, but simply a rank relative to the other patients. The judges did not consult over the ratings, but proceeded independently. An original intent to also rank the patients on the basis of "apathy-withdrawal" was not carried out, because of the lack of evidence of this affect in the interviews.

Judges: The judges varied in experience. Judge #1 was also the interviewer and the author of this thesis, and was a medical student with limited experience in interview rating. Judge #2 was an experienced research psychiatrist. The judges had previously discussed the ratings

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Judges: The judges varied in experience. Judge #1 was also the interviewer and the author of this thesis, and was a medical student with limited experience in interview rating. Judge #2 was an experienced research psychiatrist. The judges had previously discussed the [illegible]

of five other pilot patients on the basis of discomfort-involvement. Neither of the judges was aware of the steroid values or test scores of the patients at the time of rating.

Anxiety test and Depression inventory: Immediately after the interview, the patients answered a paper-and-pencil test (see Appendix I) consisting of (1)a depression inventory developed by Beck, et. al.[2] comprising 21 multiple-choice items, and (2) a condensed form of the Taylor Manifest Anxiety Scale.[63] The questionnaires were not perused or scored until evaluation of the interviews had been completed.

Comment: It was chosen to rank the patients on the basis of discomfort-involvement because of the association that had been demonstrated with preoperative cortisol levels.[50] The Taylor MAS was used because of its tendency to correlate with physiological variables,[31] particularly steroids.[19] The depression inventory was considered a reasonable example of tests of its type.

Abbreviations: On occasion in the balance of this paper the following abbreviations will be used:

$D\text{-}I_1$ = Discomfort-involvement of patient, ranked by judge #1.

$D\text{-}I_2$ = Discomfort-involvement of patient, ranked by judge #2.

MA = Score of patient on Taylor Manifest Anxiety Scale.

DP = Score of patient on depression inventory (Beck).

The Physical Parameters

Blood Samples: Five blood samples were drawn from each patient, as

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Abbreviations: On occasion in the balance of this paper the following abbreviations will be used:

D-I_1 = Discomfort-involvement of [illegible]

D-I_2 = Discomfort-involvement of patient, [illegible]

MA = Score of patient [illegible]

DP = Score of patient [illegible]

The [illegible]

Blood Samples: Five blood samples were drawn from [illegible]

described below:

#1 The first sample was drawn, when possible, at 8 a.m. on the morning of the day before operation (six patients). On occasion, the decision to operate was made by the surgeons late on the day before operation, and an 8 a.m. sample drawn earlier in the patient's hospital stay was substituted. In two cases this was drawn five days before operation, in two other cases, eight days before. The patients were never certain of the date of their operation until the afternoon of the day before surgery, so it might be expected that their psychological state would not be too dissimilar on the morning of the day before operation and on several mornings before. There is no statistically significant difference between the means of the cortisol values of the subjects having the sample taken one day before operation and those having it drawn five or eight days before. (Festinger's [18] non-parametric test for the significance of differences between means; $n = 4$, $m = 6$, $d = .25$, where it would have to be equal to or greater than 2.50 to indicate a difference significant at the 5% level of confidence.)

#2 The second sample was drawn at 8 a.m. on the morning of the day of operation.

#3 The third sample was drawn in the operating room while the patient was anesthetized, and immediately before surgical incision.

#4 The fourth sample was drawn in the operating room while the patient was still undergoing surgery, 45 minutes after sample #3.

#5 The fifth sample was drawn in the recovery room, three hours after sample #3. At this time the patient was usually conscious, but quite drowsy.

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#1 The first sample was drawn, [illegible] of [illegible] the morning of the day before operation (six patients). [illegible], the decision to operate was made by the surgeons [illegible] the day before operation, and an 8 a.m. sample drawn earlier in the [illegible] [illegible] was substituted. In two cases this was drawn five days before operation, in two other cases, eight days before. The patients were never certain of the date of their operation until the afternoon of the day before surgery, so it might be expected that their [illegible] state would not be too dissimilar on the morning of the day before operation and on several mornings before. There is no [illegible] significant difference between the means of the [illegible] of the subjects having the sample taken one day before operation and those having it drawn five or eight days before. ([illegible] [illegible] parametric test for the significance of differences between [illegible]; n = 4, m = 6, [illegible] = .[illegible], where it would have to be equal to [illegible] than 2.50 to indicate a difference significant at the [illegible] level of confidence.)

#2 The second sample was drawn at 2 a.m. on the morning of the day of operation.

#3 The third sample was drawn in the operating [illegible] the patient was anesthetized, and immediately before surgical [illegible].

#4 The fourth sample was drawn in the operating [illegible] patient was still undergoing surgery, [illegible] minutes after [illegible].

#5 The fifth sample was drawn in the [illegible], [illegible] after sample #3. At this time the patient was [illegible] quite drowsy.

At each sampling blood was drawn into two 10ml. tubes (Vacutainer) each containing 10 mg. of powdered EDTA (ethylene diamine tetraacetic acid). The blood was centrifuged immediately, and the plasma frozen at 0° to 10° F. until determination of plasma cortisol.

The cortisol determination used was a modification of the De Moor[9] fluorometric analysis, and measures 11-OH corticosteroids (cortisol + corticosterone in approximately 4:1 ratio). Nevertheless, the readings are generally considered "plasma cortisol." Duplicate samples were run, and had to agree within 10% of each other before they were accepted. The final eluate was read on a Farrand Photoelectric Fluorometer, with a 400-800 mμ primary wavelength, and a secondary filter passing 535-570 mμ. Normal 8 a.m. samples range from about 15-25 γ% using this method.

In order to rule out the possibility that medications or other impurities might have been influencing the cortisol reading, selected samples were analyzed using a Keirs Spectrophosphorimeter, scanning from 200 to 800 mμ. No evidence of contaminating fluorescence or interfering substances was noted (fig. 2).

<u>Urine Samples</u>: Twenty-four hour urine specimens were also collected from each patient on the day of surgery and the day afterwards:

U#1 from 8 a.m. on the day of surgery until 8 a.m. on the next day.

U#2 from 8 a.m. on the day after surgery until 24 hours later.

The urine was frozen and later determinations of urine 17-ketogenic steroids (KGS) were done by the regular laboratory staff of the metabolic research laboratory at the West Haven V. A. Hospital, using a method derived from

At each sampling blood was drawn into two [illegible] (Vacuum [illegible] each containing [illegible] mg. of [illegible] [illegible] acid). The blood was centrifuged immediately, and the plasma frozen at 0° to 10° F. until determination of plasma cortisol.

The cortisol determination used was a modification of the [illegible] fluorometric analysis, and measures [illegible] (cortisol + corticosterone in approximately 4:1 ratio). Nevertheless, the [illegible] are generally considered "plasma cortisol." Duplicate samples were [illegible], and had to agree within [illegible] of each other before the [illegible] accepted. The final eluate was read on a Farrand photoelectric fluorometer, [illegible] 400-[illegible] mμ primary wavelength, and a secondary filter [illegible] mμ. Normal 6 a.m. samples range from about [illegible] using this method.

In order to rule out the possibility that medications of the [illegible] impurities might have been influencing the cortisol [illegible], [illegible] samples were analyzed using a Perrin Spectrophosphorimeter, measure [illegible] 200 to 600 mμ. No evidence of contaminating fluorescence of [illegible] substances was noted (Fig. 2).

Urine Samples: Twenty-four hour urine specimens [illegible] lected from each patient on the day of surgery [illegible]

U#1 from 6 a.m. on the day of surgery until [illegible] a.m. [illegible]

U#2 from 6 a.m. on the day after surgery until [illegible] [illegible]

The urine was frozen and later determinations of urine 17-[illegible] (UCS) were done by the regular laboratory staff of the [illegible] laboratory at the [illegible] [illegible] [illegible]

the work of Norymberski,[44] and utilizing the Zimmerman reaction.[12,60] Normal standards are not established for this determination at this laboratory, but probably range about 8-22 mg/24 hours.

Proceedure

Care was taken to avoid bias in rating of D-I manifested in the interviews. None of the physical data was known to the judges at the time of rating. Plasma cortisol values had already been determined by judge #1, but the tubes had been randomly mixed and coded by another person. The urine KGS values were recorded by the laboratory personnel in a notebook, but were not read until after the ratings were made. The psychological tests (MA and DP) were not scored until after rating of the interviews was completed. In addition, the order of the interviews was, of course, known to judge #1 (the interviewer) but was concealed from judge #2, who was unaware of the patient numbers until after rating was finished. As a result, the judges read the interview transcripts in different orders.

Statistical Proceedures

Because some of the major data (D-I) was present only in the form of ranks, and also because of the unjustifiability of assuming a normal population distribution in a group subjected to an acute and similar stress, it was decided to use the rank correlation coefficient to test possible associations. The rank correlation coefficient is com-

the work of Mc[illegible], [illegible] Normal Standards for [illegible] laboratory, but probably range about [illegible] hours.

Procedure

Care was taken to avoid bias in rating of [illegible] manifestations in the interviews. None of the physical data was shown to the judges at the time of rating. Plasma cortisol values had already been [illegible] judge [illegible], but the [illegible] had been randomly mixed and coded by another person. The urine [illegible] values were [illegible] by the laboratory [illegible] in a notebook, but were not read until after the ratings were [illegible]. The psychological tests ([illegible] and [illegible]) were not scored until after rating of the interviews was completed. In addition, the order of the interviews [illegible], of course, known to judge [illegible] (the interviewer), but was concealed [illegible] judge [illegible], who was unaware of the patient numbers until [illegible] was finished. As a result, the judges [illegible] interview [illegible] in different orders.

Statistical Procedures

Because some of the major data ([illegible]) [illegible] in the form of ranks, and also because of the unjustifiability of [illegible] a normal population distribution in a group [illegible] to [illegible] similar stress, it was [illegible] to use the rank correlation coefficient test possible associations. The rank correlation coefficient is [illegible]

puted from the formula:[14]

$$r' = \frac{6\sum D^2}{n\,(n^2 - 1)}$$

where r' = the rank correlation coefficient

D = the difference between a pair of ranks for a given subject

n = the number of pairs of ranks (= the number of subjects)

Significance of the correlation coefficients was evaluated using a table computed from the data of E.G. Olds (Annals of Mathematical Statistics, 1938, 9, 133-148). Olds' tables show the distributions of sums of squares of rank differences for small numbers of individuals. (The t-distribution is an inadequate approximation of the rank difference distribution for n of 10 and below.) The use of this statistical technique does not require the assumption of a normal population distribution.[61]

RESULTS

The data measured during the course of the experiment are recorded in appendix II. Certain useful values derived from this primary information are presented in appendix III A-C, and the changes occuring in the plasma cortisol levels of each patient are charted against the time of day in figure 1. It is important to note that values standardized to an 8 a.m. level (by compensating for the normal

putes from the formula:

$$r' = \frac{6\,\Sigma\,d}{n\,(n^2 - 1)}$$

where r' = the rank correlation coefficient;

d = the difference between a pair of ranks for a given number;

n = the number of pairs of ranks (= the number of [illegible]).

Significance of the correlation coefficients was evaluated using a table computed from the data of E. G. Olds (Annals of Mathematical Statistics, 1938, 9, 133-148). Olds' tables show the distribution of sums of squares of rank differences for small numbers of individuals. (The t-distribution is an inadequate approximation of the rank difference distribution for n of 10 and below.) The use of this statistical technique does not require the assumption of a normal population distribution.[61]

RESULTS

The data measured during the course of the experiment are recorded in appendix II. Certain useful values derived from this primary information are presented in appendix III A-3, and the change occurring in the plasma cortisol levels of each patient are charted against the time of day in figure 1. It is important to note that values standardized to an 8 a.m. level ([illegible] compensating for the [illegible]

drop in plasma cortisol during the daylight hours[43]--see also fig. 1) were used in calculating most of the derived data. The reasons for using standardized values rather than measured values in comparing samples drawn at different times of day have already been discussed. In describing implications of the descriptive statistical values that will be presented, those corresponding to the commonly used level of $p < .05$ will be called "significant," those with a $p < .01$ will be called "highly significant," and those with a p between .05 and .10 will be called "suggestive" or "tendencies."

The average of the four (#2-#5) plasma cortisol samples drawn on the day of operation may be considered indicative of relative adrenocortical activity during the portion of the day including the immediate preoperative, operative, and early postoperative periods. Since the half-life of cortisol in the plasma is usually less than one hour[23] it might be expected that the relative elevations in plasma cortisol levels would be reflected in relative differences in 24 hour urinary KGS excretion, providing plasma cortisol levels during the complete 24 hour period were proportional to those during the sampled periods. Rank-order correlation of the average of standardized samples #2-#5 with urinary KGS excretion on the day of operation yields an r' of +.28, however, not significant.

The correlations of the psychological measures used with each other are recoreded in table 1. All of the tests of significance used were two-tailed --as are all the tests in this thesis unless otherwise noted--

[illegible]

[illegible]

[illegible]

except for that comparing the two D-I ratings. It is felt that a

TABLE 1. Rank-order correlations of the psychological measures with each other (for abbreviations see p.18)

$D\text{-}I_1$ with $D\text{-}I_2$	$r' = +.49$	$p < .08$ *	
$D\text{-}I_1$ with MA	$r' = +.46$	NS	
$D\text{-}I_2$ with MA	$r' = +.48$	NS	*one-tailed test; all others are two-tailed.
$D\text{-}I_1$ with DP	$r' = +.54$	NS	
$D\text{-}I_2$ with DP	$r' = +.41$	NS	

one-tailed test is appropriate in this instance, because only a positive correlation would have been accepted as indicating that both judges were rating the same phenomenon in the same manner. It can be seen that there is a tendency for the ratings of discomfort-involvement made by judge #1 to correspond to those made by judge #2. None of the other psychological measures are even suggestively correlated.

Scores on the MA scale showed a wide distribution (range 1-31 out of a maximum possible score of 50) with an average score of 12, but the depression inventory (DP) yielded a narrow range of scores, running only from 0 to 6, and were very low, averaging 2.8 out of a possible maximum of 62. (appendices I, II)

Correlations of the individual plasma cortisol samples with psychological measures are shown in table 2. Although sample #1 was taken prior to the time of interview in all patients, and very much prior to interview in four of them (for justification for combinging

TABLE 1. Rank-order correlations of the [illegible] measures with each other (for [illegible]).

$D-I_1$ with $D-I_2$	$r = +.[illegible]$	[illegible]
$D-I_1$ with [illegible]	$r = +.[illegible]$	[illegible]
$D-I_2$ with [illegible]	$r = +.[illegible]$	[illegible]
$D-I_1$ with [illegible]	$r = +.[illegible]$	[illegible]
$D-I_2$ with [illegible]	$r = +.[illegible]$	[illegible]

one-tailed test is appropriate in this instance, because only a positive correlation would have been accepted as indicating that the judges were rating the same phenomenon in the same manner. It can be seen that there is a tendency for the ratings of discomfort-involvement made by judge [illegible] to correspond to those made by [illegible]. Some of the other psychological measures are even suggestive of correlation.

Scores on the [illegible] scale showed a wide distribution (range [illegible]) out of a maximum possible score of [illegible] with [illegible], but the depression inventory ([illegible]) [illegible] a narrow range of scores, [illegible] from [illegible] to [illegible], and were very low, averaging [illegible] possible maximum of [illegible]. (appendices [illegible], [illegible])

Correlations of the individual [illegible] continuous [illegible] psychological measures are shown in table [illegible]. Although [illegible] taken prior to the time of interview in [illegible] patients, [illegible] prior to interview in four of them (for [illegible]

these samples, see p. 19) it can be seen that there is a marked re-

TABLE 2. RANK-ORDER CORRELATIONS OF INDIVIDUAL CORTISOL SAMPLES WITH PSYCHOLOGICAL MEASURES

	$D\text{-}I_1$	$D\text{-}I_2$	MA	DP
(#1) 8 a.m. one, five or eight days preop.	+.32(NS)	+.86($p<.01$)	+.44(NS)	+.25(NS)
(#2) 8 a.m. on morning of op.	-.08(NS)	-.06(NS)	-.59($p<.08$)	-.40(NS)
(#3) just before incision	+.31(NS)	+.31(NS)	+.05(NS)	-.39(NS)
(#4) 45 minutes after #3	-.21(NS)	-.23(NS)	+.07(NS)	-.45(NS)
(#5) 3 hours after #3	-.26(NS)	-.38(NS)	-.65($p<.06$)	-.15(NS)

lationship between $D\text{-}I_2$ and the level of plasma cortisol in the first blood sample. Also to be noted is the tendency for MA to inversely related to the second and fifth blood samples (the first and the last on the day of operation.)

Correlations of the 24 hour urine ketogenic steroid excretion with the psychological measures are presented in table 3. It can be seen that

TABLE 3 Rank-order correlations of 17 KGS (24 hour) on op. day with psychological measures

KGS with $D\text{-}I_1$	$r' = +.29$	NS
KGS with $D\text{-}I_2$	$r' = +.01$	NS
KGS with MA	$r' = +.54$	NS
KGS with DP	$r' = -.13$	NS

These samples, see p. 49) [illegible]

TABLE 2. RANK-ORDER CORRELATIONS OF INDIVIDUAL [illegible] WITH PSYCHOLOGICAL MEASURES

	D-I$_5$	D-I$_5$	MA	[illegible]
(#1) 8 a.m. one, five or eight days preop.	+.[illegible](NS)	+.[illegible](p[illegible])	+.[illegible](NS)	+.[illegible](NS)
(#2) 8 a.m. on morning of op.	-.68(NS)	-.[illegible](NS)	-.[illegible](NS)	-.[illegible](NS)
(#3) just before incision	+.31(NS)	+.[illegible](NS)	+.[illegible](NS)	-.[illegible](NS)
(#4) 45 minutes after #3	-.[illegible](NS)	-.[illegible](NS)	+.[illegible](NS)	-.[illegible](NS)
(#5) 3 hours after #3	-.26(NS)	-.[illegible](NS)	-.[illegible](NS)	-.[illegible](NS)

lationship between D-I$_5$ and the level of plasma cortisol in the first blood sample. Also to be noted is the tendency for an [illegible] related to the second and fifth blood samples (the first and the last on the day of operation).

Correlations of the [illegible] the psychological measures are presented in table [illegible]. [illegible]

TABLE 3. Rank-order correlations of [illegible] (#2 [illegible]) on [illegible] with psychological measures

RGS with D-I$_5$	r' = +.2[illegible]	NS
RGS with D-I$_5$	r' = -.[illegible]	NS
RGS with MA	r' = -.[illegible]	NS
RGS with DP	r' = -.[illegible]	NS

none of the correlations is significant.

Use of the average of samples #2 through #5 as an indication of the relative adrenocortical activity during the operative and immediate preoperative and postoperative periods has been discussed above. Correlation of this average with the psychological measures (table 4) shows

TABLE 4 Rank-order correlation of average standardized cortisol levels (#2+#3+#4+#5/4) on op day with psychological measures

Average with D-I_1	$r' = -.02$	NS
Average with D-I_2	$r' = -.19$	NS
Average with MA	$r' = -.59$	$p < .08$
Average with DP	$r' = -.23$	NS

a suggestive inverse relationship to the scores on the Taylor MAS.

It can be seen in appendix III that 8 a.m. plasma cortisol levels on the morning of operation average 5.2γ% lower than those from 8 a.m. on the day(s) before operation. This calculated difference is not, however, statistically significant ($t = 1.79$; $p > .10$).

Other changes in plasma cortisol levels, those on the day of operation, may be derived from the data in appendices III A, B, and C. The only highly consistent change in adrenal activity found was a net rise, usually pronounced, between sample number 3 (just before operation) and sample number 5 (three hours after the beginning of operation). Only one out of the ten patients showed a drop in plasma cortisol over this period (patient #3). Including all patients, the change in plasma cortisol during this three hour period averaged an actual rise of +15.0γ%, and an effective change of +18.4γ% (when

name of the correlations is significant.

Use of the average of samples [illegible] through [illegible] as an indication of the relative adrenocortical activity during the operative and [illegible] preoperative and postoperative periods has been [illegible]. Correlation of this average with the psychological measures (table 4) shows

TABLE 4. Rank-order correlation of average [illegible] cortisol levels ([illegible]) on [illegible] with psychological measures

Average with [illegible]	r' = -.[illegible]	[illegible]
Average with [illegible]	r' = -.[illegible]	[illegible]
Average with [illegible]	r' = -.[illegible]	[illegible]
Average with [illegible]	r' = -.[illegible]	[illegible]

a suggestive inverse relationship to the scores on the [illegible].

It can be seen in appendix III that [illegible] cortisol [illegible] on the morning of operation average [illegible] lower than those from [illegible] on the day(s) before operation. This calculated difference is not, however, statistically significant ([illegible]).

Other changes in plasma cortisol levels, those on the day of operation, may be derived from the data in appendices III [illegible], and C. The only highly consistent change in [illegible] activity [illegible] a net rise, usually pronounced, between sample number [illegible] ([illegible] operation) and sample number 5 (three hours after the beginning of operation). Only one out of the ten patients showed a [illegible] cortisol over this period (patient [illegible]). [illegible] change in plasma cortisol during this [illegible] actual rise of [illegible], [illegible] effective change of [illegible]

standardized values are used in the calculation). Both changes are statistically highly significant; using the t-test corrected for correlated data, the results are:

for actual change: $t = 3.36$ $p < .01$

for effective change: $t = 3.94$ $p < .01$.

It is of interest that patient #3, apart from being the only patient who did not raise his plasma cortisol levels from sample #3 to sample #5, was also unique in having the highest actual cortisol level at the onset of operation. This preponderant tendency toward elevated plasma corticosteroids after surgery is fully in accord with the findings of the research described in the Introduction.

None of the other changes observed in cortisol levels on the day of operation was consistent. During the period between 8 a.m. on the morning of operation (sample #2) and the beginning of operation (sample #3) the cortisol levels may either rise or fall, but the change during the wait for surgery may be shown to be significantly related to the length of time the patient had to wait: $r' = +.68$ ($p < .04$). The longer the patient has to wait for the beginning of surgery on the day of operation, then, the more probable it is that his plasma cortisol levels will rise higher (or fall less) by the time the operation begins. No previous report of this relationship has been found in the literature.

During the first 45 minutes after the onset of operation (sample #3 to sample #4) the plasma cortisol levels may again either rise or fall over a wide range of values (+15.0 γ% to -8.9 γ%). It can be demonstrated that subjects having higher

cortisol levels at the beginning of operation tend to drop their levels more during this period, while those beginning with lower levels have a greater tendency toward elevation. The rank-order correlation of sample #3 with this initial change during operation is highly significant: $r' = -.91$ ($p < .01$). This same initial steroid change is unrelated to the cortisol levels on the morning of operation (sample #2): $r' = -.38$ (NS).

Correlations of changes in plasma cortisol on the day of operation and changes in 24 hour urine KGS excretion with the psychological measures are shown in table 5. Although none of the

TABLE 5 Rank-order correlations of steroid changes with psychological ratings and tests

	$D\text{-}I_1$	$D\text{-}I_2$	MA	DP
waiting change (#2 to #3)	+.13(NS)	-.03(NS)	+.37(NS)	-.29(NS)
rate of waiting change(app. IIIB)	+.30(NS)	+.23(NS)	+.50(NS)	.00(NS)
initial op. change (#3 to #4)	-.53(NS)	-.55($p < .10$)	-.01(NS)	+.11(NS)
three-hour change (#3 to #5)	-.32(NS)	-.54(NS)	-.27(NS)	+.09(NS)
% three hour change(app. IIIC)	-.41(NS)	-.46(NS)	-.43(NS)	+.21(NS)
drop (-) in 24 hr. KGS, op. day to next	+.41(NS)	+.10(NS)	+.12(NS)	-.06(NS)

correlations ~~are~~ is statistically significant, one relationship is suggestive, that of the inverse correlation between D-I as rated by

judge #2 and the initial change in steroid levels with operation.

Correlations that are statistically significant or suggestive are summarized below (table 6).

TABLE 6 Summary of significant and suggestive statistical data

Items related	relationship (+ or -)	value	p<
$D-I_1$ and $D-I_2$	+	r' = +.49	.08
samples #3 and #5 (three hour) change			
actual		+15.0%	.01
effective		+18.4%	.01
waiting time and waiting rise	+	r' = +.68	.04
preincision level (#3) with initial change (#3 to #4)	-	r' = -.91	.01
sample #1 with $D-I_2$	+	r' = +.86	.01
sample #2 with MA	-	r' = -.59	.08
sample #5 with MA	-	r' = -.65	.06
average plasma cortisol on op day with MA	-	r' = -.59	.08
$D-I_2$ with initial change (#3 to #4)	-	r' = -.55	.10

DISCUSSION

It is well known that physiological changes often accompany intense emotional states. Whether emotion originates in the mind, and is only secondarily manifested physically[16] or is on the other hand "cortically perceived but physiologically determined"[32] is an unsolved problem, but it is certainly possible at this time to study the changes that take place in the body concomitant with emotional expression.

One such association was the starting-point of this study, namely, the demonstrated association of elevated steroid levels with preoperative emotional states.[22,50] Because both psychological and surgical stress cause increased levels of plasma cortisol, it was the expectation in beginning this work that they would tend to summate, or perhaps even act synergistically, and it was anticipated that the more anxious, involved, or generally distressed preoperative patients would tend to have a greater production of steroids in response to surgery than less disturbed patients. It has been demonstrated by Steenberg[62] that a postoperative stimulus to cortisol production (ACTH injection) appeared to be affected synergistically by the preceeding surgery, and resulted in a greater response to stimulus than in unoperated patients. If an ACTH stimulus could summate with already elevated cortisol levels as the result of preceeding surgery, then it seemed at least possible

that a preceeding ACTH stimulus due to greater emotional disturbance might summate with the subsequent adrenocortical response to surgical trauma.

One of the subsidiary expectations, based on the data of Franksson and Gemzell[22] was that steroid levels would be higher on the morning of operation than they were on the mornings of earlier days. Although the measurements made in this experiment do not directly contradict their findings (since the drop of average steroid levels occurring between the earlier samples and the morning of surgery was not statistically significant) they do fail to support their results. No obvious explanation of this discrepancy is apparent, but it should be remembered that other workers also have failed to find cortisol levels on the morning of operation elevated above normal.[36,66]

The association of high degrees of discomfort-involvement with elevated cortisol levels on the day before operation reported by Price et. al.[50] was strongly supported by the highly significant correlation of sample #1 with the D-I ratings of the more experienced judge. It is interesting that despite differences in method of rating (relative ranking used here, eight-point scale used by Price) and in collection of samples (four out of ten of this study's first samples taken earlier than one day before operation) such a strong confirmation of the earlier findings is obtained. In both instances, the blood samples were drawn before

the interview, and it may be that the precise number of days before surgery is not an important factor as long as the patient's state of anticipation is approximately the same. Also striking is the lack of correlation of D-I with the cortisol levels on the morning of operation, in contrast to the strong relationship noted with levels just one to several days before. The possibility of anticipated relief, or some other change of attitude towards the impending surgery occurring on the morning of surgery might be responsible. The feeling of a measure of relief at finally facing a feared event with the expectation of having it over with is a common one, and may be shared by surgical patients on the morning of their operation.

The depression inventory used[2] did not correlate at even suggestive levels with any other measures, and the scores were so low and clustered as to make it unlikely that it would be of much help in differentiating the psychological state of one patient from another. This may in part have been the result of an actual low incidence and degree of depression among the preoperative patients. Indeed, it was originally planned to include an appraisal of "apathy-withdrawal" in the ratings of the interviews, but this was abandoned because of lack of occurrence in the interview data. But this, in turn, may have been influenced by the conduct of the interviews, which were more geared to reveal anxiety than depression.

The data indicate that in response to inguinal herniorraphy

under cyclopropane anesthesia, there is a highly significant and relatively uniform elevation of plasma cortisol levels within three hours, that does not correlate significantly with any of the psychological measurements. In the abscence of evidence to the contrary, it may be concluded that this elevation is the result of anesthesia and surgical trauma, probably primarily the latter. The lack of any even suggestive correlations with psychological data of the three hour steroid change, and of both individual steroid samples (#3 and #4) taken while the patient was unconscious, suggests that the narcosis of anesthesia interrupts direct psychological effects on the adrenal cortices during operation. It might be interesting to compare these data with similar information obtained from patients undergoing operation under spinal anesthesia, which might be expected to block some of the effects of physical trauma on adrenocortical activity, but not to interfere with psychological influences on ACTH secretion. Psychological factors may help to account for some of the diverse findings concerning the adrenal response of spinal-anesthetized patients to surgery.

The data also show a significant correlation of waiting time with the rise (or lack of fall) in steroid levels during that time. Since no blood samples were taken at the beginning of anesthesia, it is not possible absolutely to rule out anesthesia as the cause of these "waiting time" changes, or to separate any

changes occurring during the wait from those in the first 10 minutes of anesthesia. It is felt that it is quite unlikely, however, that a large proportion of these changes (in two cases, rises even larger than the rise in three hours after incision) could have been the result of anesthesia itself, because (1) the time involved in presurgical anesthesia was probably too short to allow a great change to occur,[36] (2) pentothal and cyclopropane are not known to cause any significant changes in steroid levels, particularly in the first 20 minutes,[66] and (3) in none of the patients operated on within 45 minutes of the 8 a.m. sample (five out of ten) was there more than a minimal rise in steroids by the time surgery was begun, even though the anesthesia was identical. These results suggest that any person, irrespective of his normal tendency toward anxiety or discomfort-involvement, will be likely to have elevations of his plasma cortisol at the beginning of operation if he has to wait for surgery for a relatively long time on the day of operation.

The change occurring in the cortisol levels during the first 45 minutes of surgery (#3 to #4) showed a marked inverse correlation ($r' = -.91$) with the level at the beginning of surgery (#3). These findings conform almost literally to Wilder's Law of Initial Values,[69] which states that the higher a prestimulus level, the smaller the tendency to rise with exciting stimuli, and the greater the tendency to drop with inhibiting stimuli. Although the Law of Initial Values is generally considered an "empirical law,"[69] in this specific

case there is probably enough known about regulatory factors to enable a more specific explanation to be suggested. Assuming normal metabolism and excretion of cortisol during early surgery, there are three main factors that may determine what the initial steroid response will be: (1) a central, psychologically-influenced action on the pituitary to promote the release of ACTH, (2) the normal inhibitory effects of circulating cortisol, which can completely halt the release of ACTH temporarily if high enough,[23] (3) the early physical trauma of anesthesia and surgery, tending to cause the release of ACTH --found to be maximal about one-half hour after the beginning of surgery[7]-- by neurohumoral reflexes. (1) and (3) tend to cause elevation of cortisol levels in the blood, while (2) tends to cause a drop. (Since the half-life of cortisol in the blood is short, normally about one hour,[23] it is possible for a considerable drop to occur within 45 minutes as a result of inhibited stimuli alone, without postulating abnormally rapid removal from the bloodstream.) At the beginning of surgery, factor (1) will most likely no longer be operative, because of the narcosis of anesthesia. Factor (3) will depend on the severity of the operation, and will probably not be initially very great in a herniorraphy. Therefore it might be expected that the initial change in plasma cortisol levels will tend to be dependent to a significant degree on the levels of cortisol already present, which is precisely what is found. The suggestive correlation of the

initial change with D-I_2 (also inverse) may reflect the contribution of D-I to the individual's preoperative cortisol level (sample #3), even though correlation of D-I with the preincisional level itself may have been masked by individual variations in basal physiological activity and reactiveness. Thus the drop (if it occurs) in the initial period of surgery may reflect two factors, both suggested by the statistical data: First, a drop primarily determined by the inhibiting levels of cortisol present in the blood when other factors are relatively minimal, and second, a drop directly related to the strength of the D-I stimulus that is lost with the narcosis of surgical anesthesia.

Additional evidence suggesting the importance of psychological factors in affecting the preincisional cortisol level, at least potentially, may be found in the case of the one patient in the series who did not show a net rise in cortisol levels by three hours after incision (patient #3). This patient described a morbid fear of hypodermic needles, and also had extraordinarily high levels of cortisol when he was conscious. Although it was felt at the time of interview that the patient's assertion that he would "rather get an operation than a needle" was just another example of displacement as a means of denial,[30] further study of the transcript of the interview shows this fear to be rather deep-rooted, going back to terrifying experiences of inoculation while living in the "county home." Although a causal relationship cannot be proven, this

case may at least serve as a model of a hypothetical means by which preoperative emotional state may alter the adrenal response to physical trauma.

It remains to account for the suggestive inverse correlations of the TMAS with cortisol levels in samples #2, #5, and average plasma cortisol on the day of operation (#2+#3+#4+#5/4). The fact that there are no similar correlations with the individual samples drawn when the patient was unconscious emphasizes the possibility that there may be a significant relationship between some psychological function reflected in the TMAS and plasma cortisol.

At this point it may be worthwhile to raise the question of what psychological functions are measured by a test such as the TMAS, and what its relation to the evaluation of interview material may be. Can it be assumed that the test measures "anxiety" merely because it includes the word in its title? According to Taylor, the scores on the TMAS "tend to remain constant over relatively long periods of time."[63] This, in itself, would tend to refute the assumption, since anxiety in most persons is a considerably variable state. Upon examining the questions in the test (appendix I, pp. 5'-6') it can be seen that they deal with habitual feelings and reaction-patterns of the individual, rather than with the way he is feeling at the time he takes the test. Can the test, then, be said to show how easily and often an individual manifests anxiety (as implied in its title) rather than anxiety itself? Even

this statement would be inaccurate, for most of the questions deal with manifestations hardly unique to anxiety, such as sleep disturbance, crying, feeling inadequate, and restlessness, as well as sixteen questions (out of fifty) that seem to reflect the degree of physiologic responsiveness (tiredness, blushing, headache, tremor, bowel disturbances, vasomotor instability) to psychological states rather than the manifestation of any particular emotion. It can thus be seen that one should not expect the scores on the TMAS to reflect what might be rated as anxiety on the basis of an interview. It would seem that Taylor's test is as much a test of the ease of developing mental and physical manifestations of "discomfort-involvement" as it is anything else.

With the realization that the TMAS tests something different from what it purports to test, together with the idea of anticipated relief, mentioned above, it may be possible to suggest an explanation of the correlations with MA that were found. It may be that individuals with higher scores on the TMAS are those who tend to resolve psychological conflicts by psychosomatic means, and thereby subconsciously become accustomed to expect release of psychological tensions by physical routes. Thus it might be expected that individuals with higher scores on the TMAS might paradoxically become better able to cope with the nature of their danger as the physical threat becomes more imminent. From what is known about psychological states and steroid levels, it is likely that an individual will have lower

steroid levels as his ability to cope with his situation improves,[54] even if the increased security is at the expense of using "pathological" mechanisms.

The overall findings of changes in plasma cortisol levels on the day of operation do not support the expected relationship of summation of the effects of preoperative psychological stress and surgical stress on the adrenal cortex. It would be justifiable, on the basis of the results of this study, to reject Hypothesis I (p. 14) but Hypothesis II cannot be considered to have been adequately tested, because of insufficient data gathered by the test of depression and techniques of interview used. The results do support the concept that psychological factors may influence the adrenocortical response to physical trauma, although in a more complicated fashion than had been anticipated. It appears that Wilder's Law of Initial Values, in this instance explainable by what is known of pituitary-adrenal relationships, is a pivotal factor, and perhaps the only means by which psychological state can modify physiological responses when the individual is unconscious. If the psyche "leaves" the body in a state of excitement relative to the function being discussed, it is then less capable of responding to additional stimuli that would ordinarily be effective in causing a more pronounced response. "Inhibition by excitation"[69] is the key concept. Of course, this thesis reports no data that would indicate broader application

of the Law of Initial Values than to adrenal-cortical function, but it should serve to re-emphasize the importance of this concept in psychophysiologic research.

If an impending surgical operation always represents a real or imagined danger (or both) it also represents a stimulus that can possibly modify the physiologic response to the intervention itself. Whether or not the modification of the physiologic response may be in itself physiologically significant it is not possible to say. Patient #3--possibly because of psychological causes--had an inversion of the usual response to operation, yet similar responses are known to occur in uncomplicated operations, and this patient's convalescence was quite uneventful. The modification of the adrenal response might be of more concern in more extensive and hazardous surgery, but it is quite possible that it would be overcome completely by a greater physical trauma. Oken and Heath[45] have recently written, "there is a definite possibility that the initial-values effect operates as a determinent of prolonged stress response." This study tends to support their conjecture, and to underscore their opinion that it "deserves further study."

SUMMARY

The literature dealing with psychological factors and steroids, surgery and steroids, and psychology of preoperative surgical state is reviewed briefly. It is noted that current evidence indicates that elevated steroid levels occur with psychic turmoil of any type.

The experiment is described: ten white male patients undergoing elective unilateral inguinal herniorraphy were studied psychologically by preoperative interview and tests of " anxiety " and depression, and studied physiologically by serial plasma cortisol samples and 24 hour urinary corticosteroid (KGS) excretion. Interviews were rated on the basis of "discomfort-involvement" and without foreknowledge of any of the other experimental measurements.

All patients except one showed a marked rise in plasma cortisol levels by three hours after incision. The average rise was highly significant. Highly significant correlations were also noted between the level of the plasma cortisol at the beginning of operation and a tendency for the steroid levels to drop during the first 45 minutes of operation, as well as between one judge's rating of discomfort-involvement and the steroid levels of the patients on the days before surgery. The longer a patient waited for operation on the day of surgery, the greater tendency there was for him to have elevated cortisol levels when it began. Discomfort-involvement was suggestively related to a fall in steroids during the initial operative period. "Anxiety" test scores tended to be higher in patients with lower first and last cortisol levels on the day of operation.

The results are discussed and explanations of the results attempted. Attention is called to Wilder's concept of the Law of Initial Values, and the process of "inhibition by excitation" is discussed as central to the findings of this study, and easily explainable in this instance on the basis of known endocrine physiology.

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APPENDIX I PAPER-AND-PENCIL TEST ADMINISTERED FOLLOWING INTERVIEW ON NIGHT BEFORE SURGERY

THIS IS A CONFIDENTIAL QUESTIONNAIRE. Your answers will be used for research purposes only, and will not be associated with your name.

Name _____

Age _____ Birth date _____

Date _____

THE DEPRESSION INVENTORY WAS SCORED BY ADDING THE NUMBERS THAT WERE CIRCLED IN ANSWERING THE QUESTIONS. MAXIMUM POSSIBLE: XXX 62 XXX

THE TMAS WAS SCORED BY ADDING THE NUMBER OF ANSWERS CO-INCINDENT WITH THE KEY (SEE LAST TWO PAGES OF TEST). MAXIMUM POSSIBLE: XXX 50 XXX

Part I. Circle the one statement in each group that is closest to your own feelings.

A. 0 I do not feel sad.
1 I feel blue or sad.
2a I am blue or sad all the time and I can't snap out of it.
2b I am so sad or unhappy that it is very painful.
3 I am so sad or unhappy that I can't stand it.

B. 0 I am not particularly pessimistic or discouraged about the future
1a I feel discouraged about the future.
2a I feel I have nothing to look forward to.
2b I feel that I won't ever get over my troubles.
3 I feel that the future is hopeless and that things cannot improve

C. 0 I do not feel like a failure.
1 I feel I have failed more than the average person.
2a I feel I have accomplished very little that is worthwhile or that means anything.
2b As I look back on my life all I can see is a lot of failures.
3 I feel I am a complete failure as a person (parent,husband).

D. 0 I am not particularly dissatisfied.
1a I feel bored most of the time.
1b I don't enjoy things the way I used to.
2 I don't get satisfaction out of anything any more.
3 I am dissatisfied with everything.

E. 0 I don't feel particularly guilty.
1 I feel bad or unworthy a good part of the time.
2a I feel quite guilty.
2b I feel bad or unworthy practically all the time now.
3 I feel as though I am very bad or worthless.

F. 0 I don't feel I am being punished.
1 I have a feeling that something bad may happen to me.
2 I feel I am being punished or will be punished.
3a I feel I deserve to be punished.
3b I want to be punished.

G. 0 I don't feel disappointed in myself.

1a I am disappointed in myself.

1b I don't like myself.

2 I am disgusted with myself.

3 I hate myself.

H. 0 I don't feel I am any worse than anybody else.

1 I am very critical of myself for my weaknesses or mistakes.

2a I blame myself for everything that goes wrong.

2b I feel I have many bad faults.

I. 0 I don't have any thoughts of harming myself.

1 I have thoughts of harming myself but I would not carry them out.

2a I feel I would be better off dead.

2b I have definite plans about committing suicide.

2c I feel my family would be better off if I were dead.

3 I would kill myself if I could.

J. 0 I don't cry any more than usual.

1 I cry more now than I used to..

2 I cry all the time now. I can't stop it.

3 I used to be able to cry but now I can't cry at all even though I want to.

K. 0 I am no more irritated now than I ever am.

1 I get annoyed or irritated more easily than I used to.

2 I feel irritated all the time.

3 I don't get irritated at all at the things that used to irritate me.

L. 0 I have not lost interest in other people.

1 I am less interested in other people now than I used to be.

2 I have lost most of my interest in other people and have little feeling for them.

3 I have lost all my interest in other people and don't care about them at all.

M. 0 I make decisions about as well as ever.

1 I am less sure of myself now and try to put off making decisions.

2 I can't make decisions any more without help.

3 I can't make any decisions at all anymore.

N. 0 I don't feel I look any worse than I used to.

1 I am worried that I am looking old or unattractive.

2 I feel that there are permanent changes in my appearance and they make me look unattractive.

3 I feel that I am ugly or repulsive looking.

O. 0 I can work about as well as before.

1a It takes extra effort to get started at doing something.

1b I don't work as well as I used to.

2 I have to push myself very hard to do anything.

3 I can't do any work at all.

P. 0 I can sleep as well as usual.

1 I wake up more tired in the morning than I used to.

2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.

3 I wake up early every day and can't get more than five hours sleep.

Q. 0 I don't get any more tired than usual.

1 I get tired more easily than I used to.

2 I get tired from doing anything.

3 I get too tired to do anything.

R. 0 My appetite is no worse than usual.

1 My appetite is not as good as it used to be.

2 My appetite is much worse now.

3 I have no appetite at all any more.

S. 0 I haven't lost much weight, if any, lately.

1 I have lost more than five pounds.

2 I have lost more than ten pounds.

3 I have lost more than fifteen pounds.

T. 0 I am no more concerned about my health than usual.

1 I am concerned about aches and pains or upset stomach or constipation or other unpleasant feelings in my body.

2 I am so concerned with how I feel or what I feel that it's hard to think of much else.

3 I am completely absorbed in what I feel.

U. 0 I have not noticed any recent change in my interest in sex.

1 I am less interested in sex than I used to be.

2 I am much less interested in sex now.

3 I have lost interest in sex completely.

END OF PART ONE

Part II. Mark after each statement below whether it is true about you (T) or false (F).

1. I do not tire quickly. F
2. I am often sick to my stomach. T
3. I am about as nervous as other people. F
4. I have very few headaches. F
5. I work under a great deal of strain. T
6. I cannot keep my mind on one thing. T
7. I worry over money and business. T
8. I frequently notice my hand shakes when I try to do something. T
9. I blush as often as others. F
10. I have diarrhea("the runs") once a month or more. T
11. I worry quite a bit over possible troubles. T
12. I practically never blush. F
13. I am often afraid that I am going to blush. T
14. I have nightmares every few nights. T
15. My hands and feet are usually warm enough. F
16. I sweat very easily even on cool days. T
17. When embarrassed I often break out in a sweat which is very annoying. T
18. I do not often notice my heart pounding and I am seldom short of breath. F
19. I feel hungry almost all the time. T
20. Often my bowels don't move for several days at a time. T
21. I have a great deal of stomach trouble. T
22. At times I lose sleep over worry. T
23. My sleep is restless and disturbed. T
24. I often dream about things I don't like to tell other people. T
25. I am easily embarrassed. T
26. My feelings are hurt easier than most people. T
27. I often find myself worrying about something. T
28. I wish I could by as happy as others. T
29. I am usually calm and not easily upset. F
30. I cry easily. T
31. I feel anxious about something or someone almost all of the time. T
32. I am happy most of the time. F
33. It makes me nervous to have to wait. T

34. At times I am so restless that I cannot sit in a chair for very long. T
35. Sometimes I become so excited that I find it hard to get to sleep. T
36. I have often felt that I face so many difficulties that I could not overcome them. T
37. At times I have been worried beyond reason about something that really is not matter. T
38. I do not have as many fears as my friends. F
39. I have been afraid of things or people that I know could not hurt me. T
40. I certainly feel useless at times. T
41. I find it hard to keep my mind on a task or job. T
42. I am more self-conscious than most people. T
43. I am the kind of person who takes things hard. T
44. I am a very nervous person. T
45. Life is often a strain for me. T
46. At times I think I am no good at all. T
47. I am not at all confident of myself. T
48. I times I feel that I am going to crack up. T
49. I don't like to face a difficulty or make an important decision. T
50. I am very confident of myself. F

END OF QUESTIONNAIRE

DO NOT WRITE BELOW THIS LINE

MAXIMUM SCORES:

DF: 62 RDF: _____

MA: 50 RMA: _____

APPENDIX II: PRIMARY DATA (RANKS ARE IN PARENTHESIS)

patient & date of operation	sample time(EST) & days before op of sample #1	plasma cortisol (γ %)	24 hr.urine KGS (mg/24 hr.) U#1	U#2	$D\text{-}I_1$	$D\text{-}I_2$	MA	DP
1	#1 8:00 a.m.(1)	22.0	29.7	26.0	(4)	(2)	14	6
(2/6/64)	#2 8:00 a.m.	9.7	(4)	(5)			(3)	(1.5)
	#3 2:12 p.m.	22.9						
	#4 2:57 p.m.	14.9						
	#5 5:12 p.m.	34.2						
2	#1 8:00 a.m.(1)	17.2	21.2	10.9	(1)	(7)	6	3.5
(2/12/64)	#2 8:00 a.m.	20.9	(6)	(10)			(8.5)	(4)
	#3 8:34 a.m.	19.4						
	#4 9:19 a.m.	18.0						
	#5 11:34 a.m.	45.4						
3	#1 8:00 a.m.(1)	44.8	35.1	25.0	(3)	(3)	13	3
(2/13/64)	#2 8:00 a.m.	49.3	(3)	(6)			(4)	(5.5)
	#3 8:30 a.m.	44.4						
	#4 9:15 a.m.	39.8						
	#5 11:30 a.m.	26.9						
4	#1 8:00 a.m.(5)	18.6	26.6	18.1	(9)	(9)	12	1
(2/17/64)	#2 8:00 a.m.	14.9	(5)	(8)			(5)	(7.5)
	#3 8:36 a.m.	12.9						
	#4 9:21 a.m.	23.9						
	#5 11:36 a.m.	28.3						
5	#1 8:00 a.m.(1)	37.3	38.8	34.4	(6)	(5)	10	0
(2/24/64)	#2 8:00 a.m.	23.8	(2)	(2.5)			(6)	(9.5)
	#3 1:12 p.m.	40.0						
	#4 1:57 p.m.	30.6						
	#5 4:12 p.m.	54.3						
6	#1 8:00 a.m.(8)	20.2	16.5	33.2	(7)	(8)	8	6
(3/3/64)	#2 8:00 a.m.	19.8	(8)	(4)			(7)	(1.5)
	#3 11:17 a.m.	9.2						
	#4 12:02 p.m.	23.1						
	#5 2:17 p.m.	45.0						
7	#1 8:00 a.m.(8)	21.4	14.9	14.1	(10)	(4)	1	1
(3/3/64)	#2 8:00 a.m.	22.7	(10)	(9)			(10)	(7.5)
	#3 8:35 a.m.	16.5						
	#4 9:20 a.m.	19.9						
	#5 11:35 a.m.	40.5						
8	#1 8:00 a.m.(1)	19.8	39.6	34.4	(5)	(6)	31	3
(3/26/64)	#2 8:00 a.m.	11.9	(1)	(2.5)			(1)	(5.5)
	#3 12:06 p.m.	13.5						
	#4 12:51 p.m.	22.6						
	#5 3:06 p.m.	35.3						
9	#1 8:00 a.m.(5)	38.8	15.6	20.3	(2)	(1)	17	4
(3/30/64)	#2 8:00 a.m.	14.0	(9)	(7)			(2)	(3)
	#3 8:31 a.m.	16.5						
	#4 9:16 a.m.	17.3						
	#5 11:31 a.m.	22.6						
10	#1 8:00 a.m.(1)	15.7	17.5	39.6	(8)	(10)	6	0
(3/30/64)	#2 8:00 a.m.	17.3	(7)	(1)			(8.5)	(9.5)
	#3 11:52 a.m.	24.3						
	#4 12:37 p.m.	26.2						
	#5 2:52 p.m.	37.2						
AVERAGES	#1:25.6 #4:23.6		25.6	25.6			12	2.8
	#2:20.4 #5:36.9							
	#3:21.9							

[illegible]

patient & date of operation	sample time (hr) & days before op of sample #1	[illegible]	[illegible] (mg/kg hr.)					
			U_{p1}	U_{p2}	[illegible]	[illegible]	[illegible]	[illegible]
1 (1/5/64)	#1 5:00 a.m. (1)	[illegible]	[illegible]	[illegible]	(1)	(1)	[illegible]	[illegible]
	#2 6:00 a.m.	[illegible]	(4)	(4)			(4)	(4.)
	#3 1:12 p.m.	[illegible]						
	#4 2:37 p.m.	[illegible]						
	#5 9:11 p.m.	[illegible]						
2 (2/12/64)	#1 6:00 a.m. (1)	[illegible]	[illegible]	[illegible]	(1)	(1)	[illegible]	[illegible]
	#2 6:00 a.m.	[illegible]	(4)	(4)			(4.)	(4)
	#3 [illegible] a.m.	[illegible]						
	#4 [illegible] a.m.	[illegible]						
	#5 11:[illegible] a.m.	[illegible]						
3 (2/13/64)	#1 6:00 a.m. (1)	[illegible]	[illegible]	[illegible]	(1)	(1)	[illegible]	[illegible]
	#2 6:00 a.m.	[illegible]	(3)	(4)			(4)	(4.)
	#3 6:30 a.m.	[illegible]						
	#4 [illegible] a.m.	[illegible]						
	#5 11:[illegible] a.m.	[illegible]						
4 (2/17/64)	#1 6:00 a.m. (1)	[illegible]	[illegible]	[illegible]	(1)	(1)	[illegible]	[illegible]
	#2 6:00 a.m.	[illegible]	(3)	(4)			(4)	(7.)
	#3 6:30 a.m.	[illegible]						
	#4 [illegible] a.m.	[illegible]						
	#5 11:[illegible] a.m.	[illegible]						
5 (2/24/64)	#1 6:00 a.m. (1)	[illegible]	[illegible]	[illegible]	(1)	(1)	[illegible]	[illegible]
	#2 6:00 a.m.	[illegible]	(1)	(2.3)			(4)	(4.)
	#3 1:12 p.m.	[illegible]						
	#4 1:37 p.m.	[illegible]						
	#5 [illegible] p.m.	[illegible]						
6 (3/3/64)	#1 6:00 a.m. (1)	[illegible]	[illegible]	[illegible]	(1)	(1)	[illegible]	[illegible]
	#2 6:00 a.m.	[illegible]	(1)	(1)			(1)	(4.)
	#3 11:17 a.m.	[illegible]						
	#4 12:02 p.m.	[illegible]						
	#5 2:17 p.m.	[illegible]						
7 (3/3/64)	#1 6:00 a.m. (1)	[illegible]	[illegible]	[illegible]	(1)	(1)	[illegible]	[illegible]
	#2 6:00 a.m.	[illegible]	(1)	(1)			(1)	(7.)
	#3 6:35 a.m.	[illegible]						
	#4 [illegible] a.m.	[illegible]						
	#5 11:[illegible] a.m.	[illegible]						
8 (3/26/64)	#1 6:00 a.m. (1)	[illegible]	[illegible]	[illegible]	(1)	(1)	[illegible]	[illegible]
	#2 6:00 a.m.	[illegible]	(1)	(2.3)			(1)	(4.)
	#3 12:00 p.m.	[illegible]						
	#4 12:51 p.m.	[illegible]						
	#5 [illegible] p.m.	[illegible]						
9 (3/30/64)	#1 6:00 a.m. (1)	[illegible]	[illegible]	[illegible]	(1)	(1)	[illegible]	[illegible]
	#2 6:00 a.m.	[illegible]	(1)	(1)			(1)	(1)
	#3 6:31 a.m.	[illegible]						
	#4 [illegible] a.m.	[illegible]						
	#5 11:[illegible] a.m.	[illegible]						
10 (3/30/64)	#1 6:00 a.m. (1)	[illegible]	[illegible]	[illegible]	(1)	(1)	[illegible]	[illegible]
	#2 6:00 a.m.	[illegible]	(1)	(1)			(1)	(4.)
	#3 11:[illegible]2 a.m.	[illegible]						
	#4 12:37 p.m.	[illegible]						
	#5 2:32 p.m.	[illegible]						
AVERAGES	#1:[illegible]	#4:[illegible]	[illegible]	[illegible]			[illegible]	[illegible]
	#2:[illegible]	#5:[illegible]						
	#3:[illegible]							

APPENDIX III (A-C) CALCULATED DATA (RANKS IN PARENTHESIS)

A.

patient number	plasma steroid standardized to 8 a.m. (in δ %)					average standardized cortisol on op day
#	#1	#2	#3	#4	#5	(#2-#5/4) (δ%)
1	22.0 (4)	9.7 (10)	30.5 (3)	23.1 (7)	44.4 (6)	26.9 (6.5)
2	17.2 (9)	20.9 (4)	20.2 (5)	19.9 (9)	50.7 (3)	27.9 (5)
3	44.8 (1)	49.3 (1)	45.1 (2)	41.6 (1)	32.2 (9)	42.1 (2)
4	18.6 (8)	14.9 (7)	14.7 (9)	25.8 (6)	33.7 (8)	22.3 (9)
5	37.3 (3)	23.8 (2)	46.9 (1)	38.0 (2)	63.5 (1)	43.1 (1)
6	20.2 (6)	19.8 (5)	14.1 (10)	29.1 (5)	52.7 (2)	28.9 (4)
7	21.4 (5)	22.7 (3)	17.3 (7)	21.8 (8)	45.8 (4)	26.9 (6.5)
8	19.8 (7)	11.9 (9)	19.6 (6)	29.2 (4)	43.6 (7)	23.6 (8)
9	38.8 (2)	14.0 (8)	17.2 (8)	19.1 (10)	27.9 (10)	19.6 (10)
10	15.7 (10)	17.3 (6)	30.1 (4)	32.6 (3)	45.3 (5)	31.3 (3)
Average	25.6	20.4	25.6	28.0	43.9	

B. (STANDARDIZED VALUES ARE USED IN CALCULATIONS)

PATIENT NUMBER	waiting time (min) (8 a.m. to time #3)	waiting change (#2 to #3) (δ%)	rate of waiting change (δ%/100min)	initial op change (#3 to #4) (δ%)
1	372(1)	+20.8(2)	+5.6(3)	-7.4(9)
2	34(8)	- 0.7(7)	-2.1(7)	-0.3(7)
3	30(10)	-4.2(8)	-14.0(9)	-3.5(8)
4	36(6)	-0.2(6)	-0.6(6)	+11.1(2)
5	312(2)	+23.1(1)	+7.7(2)	-8.9(10)
6	192(5)	-5.7(10)	-2.9(8)	+15.0(1)
7	35(7)	-5.4(9)	-15.4(10)	+4.5(4)
8	246(3)	+7.7(4)	+3.1(5)	+9.6(3)
9	31(9)	+3.2(5)	+10.3(1)	+1.9(6)
10	232(4)	+12.8(3)	+5.5(4)	+2.5(5)
AVERAGE	153	+5.1		

A.

patient number	plasma [illegible] standardized to a.m. (in %)					average standardized control on [illegible]
	#1	#2	#3	#4	#5	(#1-#4) (%)
1	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	(8)	(10)	(5)	(7)	(6)	(5)
2	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	(9)	(8)	(6)	(5)	(3)	(3)
3	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	(1)	(1)	(2)	(1)	(2)	(1)
4	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	(6)	(7)	(9)	(6)	(5)	(5)
5	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	(3)	(3)	(4)	(2)	(1)	(1)
6	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	(8)	(8)	(6)	(5)	(2)	(2)
7	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	(5)	(5)	(7)	(6)	(4)	(4)
8	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	(7)	(8)	(6)	(4)	(7)	(7)
9	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	(2)	(4)	(6)	(5)	(6)	(5)
10	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	(10)	(4)	(4)	(3)	(4)	(4)
Average	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	

B. (STANDARDIZED VALUES ARE SEND IN CALCULATIONS)

PATIENT NUMBER	waiting time (min) (a.m. to time #3)	waiting change (#2 to #3) (%)	rate of waiting change (%) (minutes)	[illegible] (#3 to #4) (%)
1	372(1)	+20.[illegible](1)	+[illegible](5)	[illegible]
2	34(4)	-[illegible](7)	[illegible]	[illegible]
3	30(10)	-[illegible](6)	-[illegible](9)	[illegible]
4	35(6)	-[illegible](5)	[illegible]	[illegible]
5	312(2)	+[illegible](1)	+[illegible](2)	[illegible]
6	[illegible](3)	-317(10)	[illegible]	[illegible]
7	35(7)	[illegible]	[illegible]	[illegible]
8	[illegible](3)	+[illegible](4)	+[illegible](4)	[illegible]
9	[illegible](8)	+[illegible](5)	[illegible]	[illegible]
10	[illegible](4)	+[illegible](3)	[illegible]	[illegible]
AVERAGE 153		[illegible]		

APPENDIX III (CONTINUED) CALCULATED DATA (RANKS IN PARENTHESIS)

C.

PATIENT NUMBER	LATER OP. CHANGE (#4 to #5)(γ %)	TOTAL CHANGE (3 HR.) (#3 to #5) (γ %)	TOTAL CHANGE AS % OF VALUE #3	CHANGE IN 24 hr. KGS (OP DAY TO POSTOP DAY)(MG/D)
1	+21.3(5)	+13.9(8)	+46% (8)	-3.7 (6) *
2	+32.8(1)	+30.5(2)	+151%(3)	-10.3(1)
3	-9.4 (10)	-12.9(10)	-29% (10)	-10.1(2)
4	+7.9 (9)	+19.0(5)	+129%(4)	-8.5 (3)
5	+25.5(2)	+16.6(6)	+35% (9)	-4.4 (4)
6	+23.6(4)	+38.6(1)	+274%(1)	+16.7(9)
7	+24.0(3)	+28.5(3)	+165%(2)	-0.8 (7)
8	+14.4(6)	+24.0(4)	+122%(5)	-5.2 (5)
9	+8.8 (8)	+10.7(9)	+62% (6)	+4.7 (8)
10	+12.7(7)	+15.2(7)	+50% (7)	+22.1(10)
AVERAGE	+18.4	+100%		* higher rank with greater drop

[illegible]

[illegible]

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
1	[illegible]	[illegible]	[illegible]	[illegible]
2	[illegible]	[illegible]	[illegible]	[illegible]
3	[illegible]	[illegible]	[illegible]	[illegible]
4	[illegible]	[illegible]	[illegible]	[illegible]
5	[illegible]	[illegible]	[illegible]	[illegible]
6	[illegible]	[illegible]	[illegible]	[illegible]
7	[illegible]	[illegible]	[illegible]	[illegible]
8	[illegible]	[illegible]	[illegible]	[illegible]
9	[illegible]	[illegible]	[illegible]	[illegible]
10	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

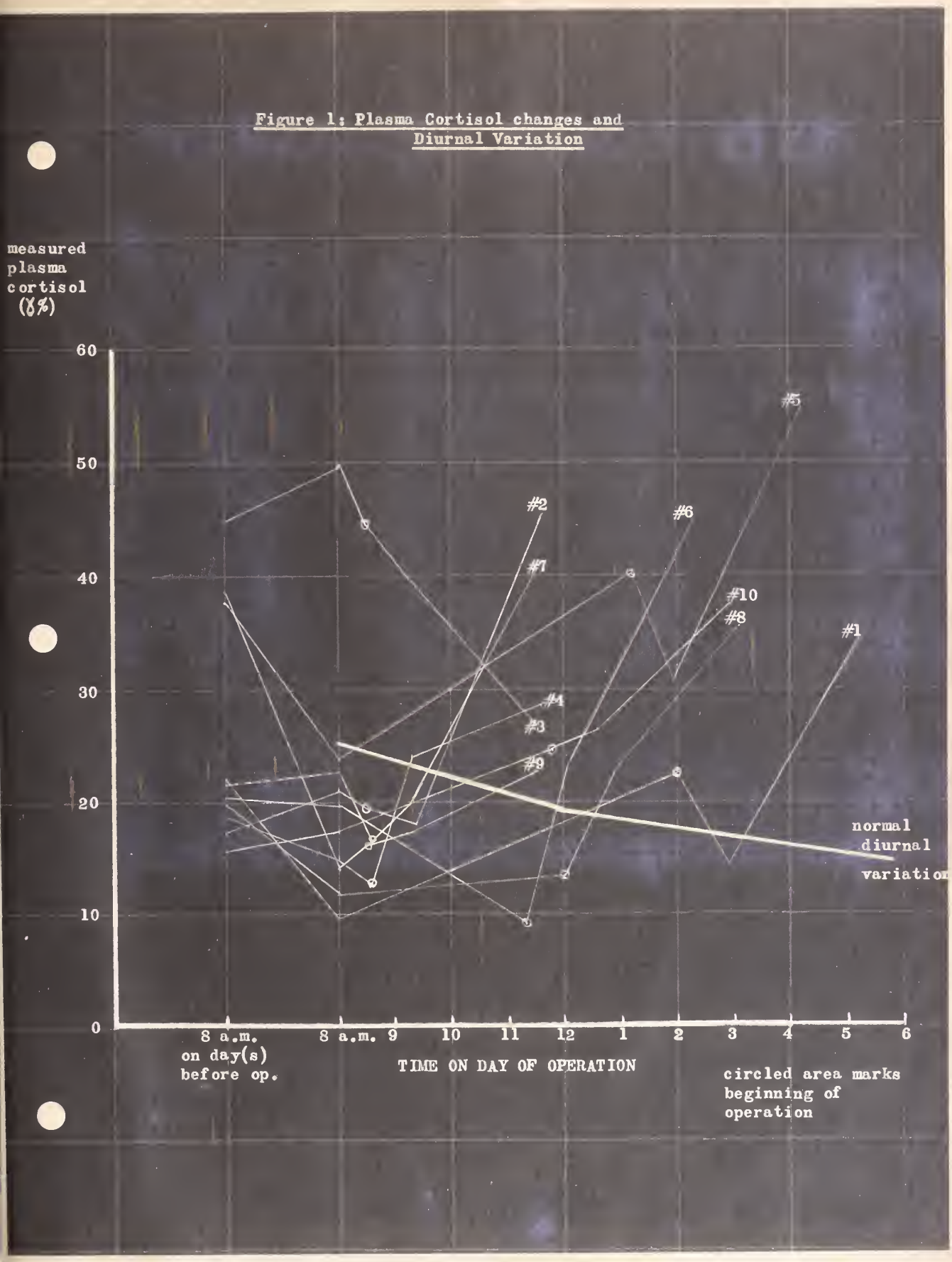
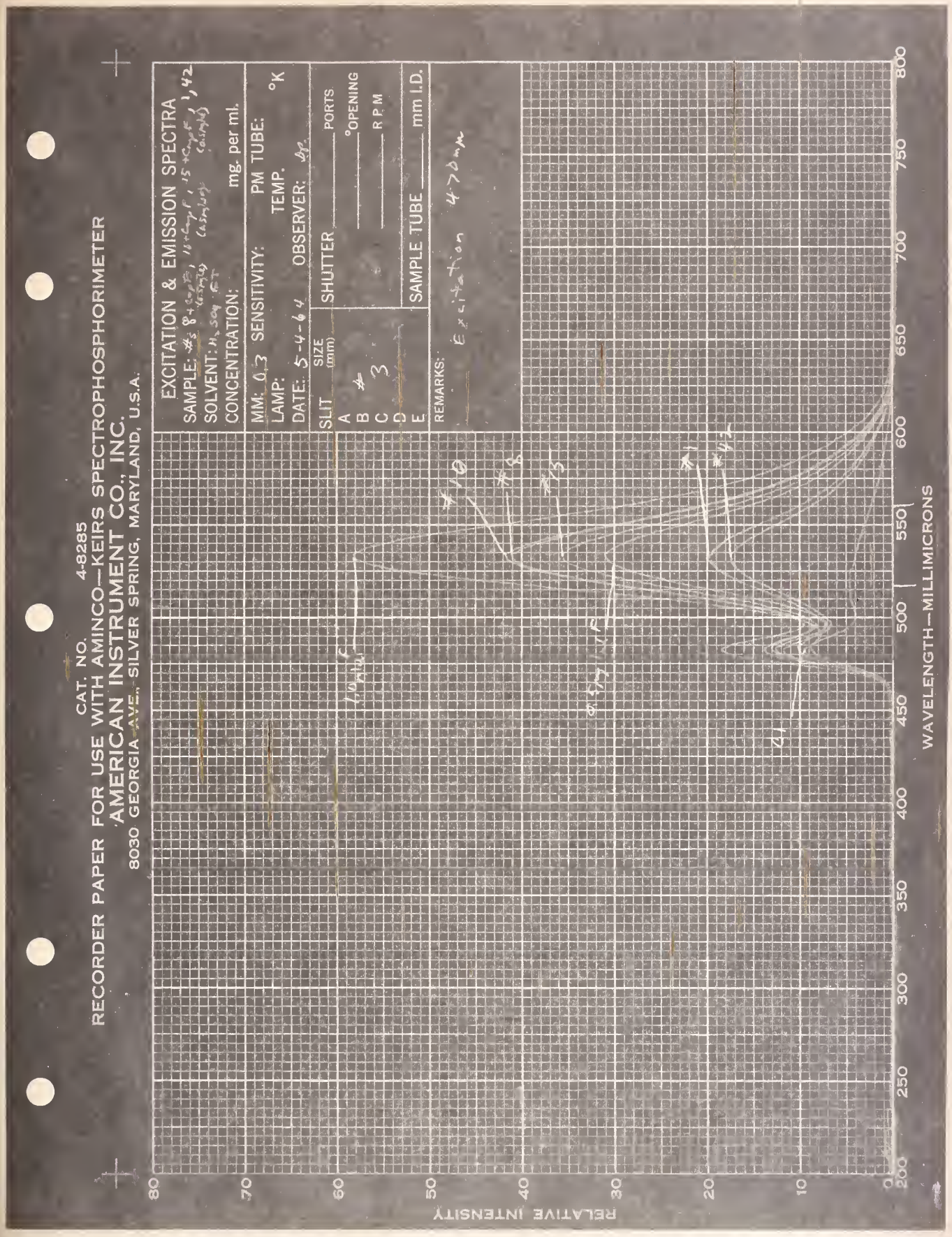


Figure 1: Plasma Cortisol changes and Diurnal Variation

FIGURE 2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